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January 11, 1999

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(Attention: Section 8(e) Coordinator)
Office of Toxic Substances
U.S. Environmental Protection Agency
401 M Street, S. W.
Washington, D. C. 20460

8EHQ-99-14356
88990000075S

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RE: TSCA Section 8(e) Submission

Alcohol Ethoxylate-Alcohol Mixture

ATTN.: TSCA Section 8(e) Coordinator

This submission is made in accordance with TSCA Section 8(e) requirements.

This provides findings communicated to us via the contract laboratory (see attached) for an acute oral toxicity study in mice on a mixture identified as SS0604.01. This test substance mixture is know to elicit a neurotoxic response. It was included in this study to characterize the response in mice using this test protocol.

In this test, 5 ml test article per kg body weight were administered neat by oral gavage once to each of 10 females. On the day of dosing, within 2 hr of dosing 7 out of 10 mice treated exhibited ataxia. Of those animals, 2 out of 10 exhibited loss of righting reaction. The onset of these clinical signs was within 21 minutes. The duration of ataxia was between 16 and 71 minutes and the duration of loss of righting reaction was between 3 and 43 minutes. All animals returned to normal appearance by 2.5 hr post-dosing. All animals continued to be observed for 14 days without any additional significant effects observed.

We have handled and will continue to handle this material with appropriate caution in our laboratory work in keeping with our standard procedures for handling all chemical substances. We will continue our practice of communicating appropriate hazard information for the test substance by both labels and MSDS.

We are requesting that the specific chemical identity of the test material be treated as confidential information in this submission. We have not publicly disclosed any business interest or plans regarding the test substance. Measures to protect confidential information include "need to know" internal restrictions within the Company, confidential disclosure agreements with potential suppliers, and confidentiality restrictions imposed upon information shared with the agency. Security at our technical centers is excellent and knowledge of R&D activities pertaining to this material has been carefully restricted to employees who have a need to know. Disclosure of the specific chemical identity of the test material would provide competitors with valuable knowledge which is not otherwise available and which could significantly reduce the competitive advantage normally associated with the development and commercialization of new products.

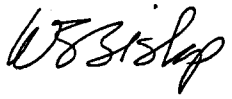
COMPANY SANITIZED
CONTAINS NO CBI

Please note that we have circled the information which we regard as legally confidential. This circled information has been deleted from a second, public display version of this submission. In the event of a proposed disclosure, notice should be given to J. C. McGregor at 513/983-6541.

If you wish further information, please contact me.

Very truly yours,

THE PROCTER AND GAMBLE COMPANY



W. E. Bishop, Ph. D.
Manager
Risk, Policy & Regulatory Sciences Dept.
Telephone: 513/627-6145

Chemical Identity/Process Description
Test Substance SS0604.01

Public Display Version

Order of Addition of Materials	CAS#	Quantity

COMPANY SANITIZED
CONTAINS NO CBI

SINGLE ORAL DOSE STUDY WITH SS0592.01, SS0604.01, SS0605.01, SS0608.01 AND 10000498 IN MICE WITH LIMITED NEUROLOGICAL ENDPOINTS

DRAFT REPORT

Study Director

Elizabeth V. Weaver, B.A., DABT

Study Completed on

To be entered later

Performing Laboratory

Procter & Gamble Non Clinical Testing Laboratory (PGNCTL)
Miami Valley Labs
11810 E. Miami River Road
Ross, Ohio 45061

PGNCTL Study No.

B99-9010

P&G DRD No.

SSBTS98.020
SAF 265-50419

Submitted to

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COMPLIANCE STATEMENT

This study was conducted in compliance with the current Good Laboratory Practice Standards as described by the United States Environmental Protection Agency, 40 CFR 792, with the exception that analysis of the test articles for concentration, homogeneity/solubility, and stability were not conducted.

_____ Date_____

Elizabeth V. Weaver, B.A., DABT
Study Director
PGNCTL

QUALITY ASSURANCE STATEMENT

I. SUMMARY

The short term oral toxicity and lethality of test articles SS0592.01, SS0604.01, SS0605.01, SS0608.01, and 10000498 were evaluated in female mice. In addition, limited neurological endpoints (ataxia and loss of righting reaction) were evaluated to determine the neurotoxicity of the test articles. A limit test was performed in which ten female mice per test article received a single oral administration of the test article at a dose of 5ml/kg body weight. Following dosing, the study animals were observed continuously for 2 hours post-dose, at 2.5, 3.0, 3.5, 4.0, 6.0, and 8.0 hours post-dose, and daily thereafter for 14 days post-dose. Animals were weighed weekly. A gross necropsy examination was performed on all study animals at the scheduled euthanasia (study day 15).

No mortality occurred during the limit test. An increase in locomotor activity was noted in 1/10 animals within 2 hours of dosing test article SS0592.01, and an injured hind limb was noted in 1/10 animals in this treatment group on study day 4 which was resolved by study day 7. Ataxia was noted in 7/10 animals and loss of righting reaction was noted in 2/10 animals within 2 hours of dosing SS0604.01. Soft feces were noted in 1/10 animals within 2 hours of dosing SS0605.01. All other animals in the above treatment groups, and all animals treated with SS0608.01 and 10000498, appeared normal throughout the study. All animals in all groups exhibiting effects within 2 hours of dosing returned to normal appearance by 2.5 hours after dosing. The signs exhibited by mice treated with SS0592.01 and SS0605.01 were not suggestive of neurotoxicity. The signs of neurotoxicity exhibited by mice treated with SS0604.01 were interpreted as transient neurotoxicity.

All animals exhibited body weight gain over the length of the study with the exception of two animals treated with SS0605.01. These animals exhibited an initial weight gain over the first week post-dose, but exhibited insignificant weight loss during the last week of study which was not considered indicative of any treatment-related health effect.

All animals survived to scheduled euthanasia on study day 15. At necropsy, unilateral ovarian cysts were noted in 2/10 and 1/10 animals treated with SS0604.01 and 10000498, respectively. These findings were considered incidental and unrelated to treatment. No other macroscopic lesions were observed in any of the animals.

Under the conditions of this limit test, the acute oral LD50s of the test articles SS0592.01, SS0604.01, SS0605.01, SS0608.01, and 10000498 was estimated to be greater than 5 ml/kg in the female mouse.

I. INTRODUCTION

This study was performed to assess the short-term toxicity, and neurotoxicity as determined by examination of the endpoints of ataxia and loss of righting reaction, of test articles SS0592.01, SS0604.01, SS0605.01, SS0608.01, and 10000498 in CD-1 female mice when administered by gavage as a single oral dose. This study is intended to provide information on the potential health hazards of the test articles with respect to oral exposure. Data from this study may serve as a basis for classification and/or labeling of the test article. This study was performed at the Procter & Gamble Non Clinical Testing Laboratory, Miami Valley Laboratories, 11810 E. Miami River Road, Ross, Ohio 45061. The protocol was signed by the Study Director on October 28, 1998. The in-life phase of the study was initiated with test article administration on October 29, 1998 and concluded with the final terminal euthanasia on November 13, 1998.

II. MATERIALS AND METHODS

A. Experimental Protocol

The study protocol is presented in Appendix A.

B. Test Article

The test articles were received from the Sponsor and identified as follows:

Test Article ID	Physical Description	Receipt Date	Expiration Date
SS0592.01	slightly yellow liquid	10/15/98	9/99
SS0604.01	opaque liquid	10/23/98	10/13/99
SS0605.01	opaque liquid	10/28/98	10/13/99
SS0608.01	slightly yellow liquid	10/22/98	10/99
10000498	colorless liquid	10/19/98	7/14/99

The test articles were stored at room temperature. The Sponsor is responsible for any necessary evaluations related to the chemical composition, purity, strength, stability and other data required by regulatory agencies.

C. Retention Sample

An approximately 2 ml retention sample of each test article was taken on study day 1 and stored at room temperature until being returned to the Sponsor Representative. Retention of these samples is the responsibility of the Sponsor Representative.

D. Test Article Disposition

After completion of the study, and upon authorization from the Sponsor Representative, remaining test articles were returned to:

Mary Marrero
F&HC PSR&AS C1N39E
Sharon Woods Technical Center
11510 Reed Hartman Highway
Cincinnati, OH 45241

E. Method of Test Article Preparation

The test articles were administered as received.

F. Animals and Animal Husbandry

1. Description, Identification and Housing

Young adult, female CD-1 mice were received at the testing facility on October 20, 1998 from Harlan Sprague Dawley, Inc., Indianapolis, IN. Upon receipt, metal ear tags displaying unique identification numbers were used to individually identify the animals. The animals were housed individually in plastic shoebox cages. Cage cards displaying the study number, animal ear tag number, sex, and treatment group color code were affixed to each cage. Housing and care were based on the standards recommended by the Guide for the Care and Use of Laboratory Animals [1].

2. Environment

Environmental control equipment was used to monitor and adjust environmental conditions as necessary to minimize fluctuations in the animal room environment. The animal room temperature and relative humidity were recorded a minimum of once daily, and the temperature and humidity ranges were 71-75°F and 37-52%, respectively. Light timers were set to maintain a 12-hour light/12-hour dark cycle. The dark cycle was interrupted for 30 and 25 minutes to remove feed and 31 and 26 minutes to prepare for dosing on study days 1 and 2, respectively. However, these interruptions are considered to have had no adverse effect on the outcome of this study. Room ventilation was set to produce approximately 10 air changes/hour.

3. Food

PMI Certified Rodent Chow #5002 (Purina Mills, Inc.) was provided ad libitum to the animals throughout the study (except during fasting). Lot # AUG 13 98 1B was used during the study. The feed was analyzed by the supplier for nutritional components and environmental contaminants. Dietary limitations for various environmental contaminants, including heavy metals, pesticides, polychlorinated biphenyls and total aflatoxin are set by the manufacturer. Within these limits, there were no environmental contaminants reasonably expected in the diet which would interfere with the conduct of this study. Results of dietary analyses (Certificates of Analysis) are provided by the manufacturer for each lot of diet. These are maintained by the PGNCTL.

4. Water

Municipal tap water following treatment by reverse osmosis was available to the animals ad libitum throughout the study. The purified water was supplied by bottle. Monitoring of the drinking water for contaminants has been conducted by the facility. Levels of contaminants which may have been present are not expected to compromise the integrity of this study. The water meets the standards specified under the EPA National Drinking Water Regulations (40 CFR, Part 141). Results of the water analyses are maintained by the facilities, and copies are maintained by the PGNCTL.

5. Acclimation

Upon receipt, the animals were removed randomly from the shipping cartons and placed into individual cages. The animals were examined by qualified personnel, identified with metal ear tags, and the animal ear tag numbers were recorded. Animals were acclimated to the laboratory conditions for four days. The animals were observed daily for overt physical or behavioral abnormalities, moribundity, and mortality.

6. Animal Selection

The animals chosen for study use were randomly selected from healthy stock animals to avoid potential bias. All animals received a detailed pretest examination prior to dosing. Females were nulliparous and nonpregnant.

III. EXPERIMENTAL DESIGN AND PROCEDURES

A. Body Weights

Individual body weights were obtained at receipt, prior to randomization (study day -1), prior to dosing on study day 1, and for all surviving animals on study days 8 and 15.

B. Randomization

On study day -1, all animals were weighed and body weights were used to perform a manual stratified randomization procedure for assignment of animals to treatment groups.

C. Dosing

Animals were fasted for 8 hours ± 47 minutes prior to dosing. On the day of dosing, fasted body weights were obtained for each animal, and individual doses were calculated based on the animals' fasted body weight. Each test article was administered at 5 ml/kg orally as a single gavage dose using a ball tipped stainless steel gavage needle attached to a syringe. Animals were returned to ad libitum feeding approximately 2 hours after dosing.

D. Clinical Observations

Study animals were observed for clinical abnormalities pre-dose, continuously for 2 hours post-dose, approximately 2.5, 3.0, 3.5, 4.0, 6.0, and 8.0 hours post-dose, and daily thereafter for 14 days post-dose. On the day of dosing, each observation interval included specific evaluations for ataxia and loss of righting reactions. General health/mortality checks were performed a minimum of twice daily (in the morning and in the afternoon).

E. Gross Necropsy

All animals survived to study termination, and surviving animals were euthanized and necropsied and the date of death was recorded. Animals were euthanized by carbon dioxide inhalation. At necropsy, the evaluations were limited to orifices, external surfaces of the body, and the cranial, thoracic, abdominal, and pelvic body cavities and their contents. Any abnormalities were documented and no tissues were retained.

IV. PROTOCOL AMENDMENTS AND DEVIATIONS

A protocol amendment was issued to correct the expiration dates of test materials SS0592.01, SS0604.01, and SS0605.01. The protocol originally listed the expiration date of test articles SS0592.01, SS0604.01, and SS0605.01 as 10/13/99, 9/99, and 9/99, respectively. Upon receipt, the test articles were indicated to have an expiration date of 9/99, 10/13/99, and 10/13/99, respectively. A second protocol amendment was issued after the issuance of the audited draft to change the Procter & Gamble DRD Number. The original number was listed as SSBTS09.020-50419. This was changed to SSBTS98.020 with an SAF category added to read SAF 265-50419. No protocol deviations occurred during this study.

V. ANALYSIS OF DATA

Body weight means and standard deviations were calculated for each treatment group.

Data for each treatment group were analyzed and an LD50 value was estimated as greater than the administered dose only if there were no deaths out of ten treated animals. No estimate of the LD50 was made if there were any deaths among the treated animals.

VI. MAINTENANCE OF RAW DATA, RECORDS AND SPECIMENS

All original data, magnetically encoded records, and the final report from this study were transferred to the PGNCTL archives (Central Records - MVL) for a period of 20 years. The Sponsor will be contacted prior to the final disposition of these items.

VII. RESULTS

A. Mortality

A mortality summary is presented in Table 1.

No mortality was observed during this study.

B. Body Weight

Individual and mean body weights and body weight gains are presented in Table 2.

All animals exhibited body weight gain over the length of the study with the exception of two animals treated with SS0605.01. These animals exhibited an initial weight gain over the first week post-dose, but exhibited a slight weight loss (0.1 to 0.4 g) during the last week of study.

C. Clinical Observations

Individual clinical observations are presented in Table 3.

For each test article, notable clinical abnormalities were observed as follows:

Test Article	Clinical Observations
SS0592.01	1/10 animals treated exhibited increased locomotor activity within 2.0 hours post-dose, but returned to normal appearance by 2.5 hours post-dose. 1/10 animals exhibited an injured hind limb on study day 4 which was resolved by study day 7. All other animals appeared normal throughout the study.
SS0604.01	7/10 animals treated exhibited ataxia within 2.0 hours post-dose, and of those animals, 2/10 exhibited loss of righting reaction. The onset of these clinical signs was within 21 minutes. The duration of ataxia was between 16 and 71 minutes, while the duration of loss of righting reaction was between 3 and 43 minutes. All animals returned to normal appearance by 2.5 hours post-dose. All other animals appeared normal throughout the study.
SS0605.01	1/10 animals treated exhibited soft feces within 2.0 hours post-dose. All other animals appeared normal throughout the study.
SS0608.01	10/10 animals appeared normal throughout the study.
10000498	10/10 animals appeared normal throughout the study.

D. Gross Necropsy Observations

Individual gross necropsy observations are presented in Appendix B.

A summary report by the study pathologist is in Appendix B. Unilateral ovarian cysts were noted in 2/10 and 1/10 animals treated with SS0604.01 and 10000498, respectively. No other macroscopic lesions were observed in any of the animals.

VIII. CONCLUSIONS

No mortality occurred during the study. An increase in locomotor activity was noted in 1/10 animals within 2 hours of dosing test article SS0592.01, and an injured hind limb was noted in 1/10 animals in this treatment group on study day 4 which was resolved by study day 7. Ataxia was noted in 7/10 animals and loss of righting reflex was noted in 2/10 animals within 2 hours of dosing test article SS0604.01. Soft feces were noted in 1/10 animals within 2 hours of dosing test article SS0605.01. All other animals in the above treatment groups, and all animals treated with SS0608.01 and 10000498, appeared normal throughout the study. All animals in all treatment groups exhibiting effects within 2 hours of dosing returned to normal appearance by 2.5 hours after dosing. The signs exhibited by mice treated with SS0592.01 and SS0605.01 are not suggestive of

neurotoxicity. The signs of neurotoxicity exhibited by mice treated with SS0604.01 are indicative of transient neurotoxicity.

All animals exhibited body weight gain over the length of the study with the exception of two animals treated with SS0605.01. These animals exhibited an initial weight gain over the first week post-dose, but exhibited insignificant weight loss during the last week of study which is not considered indicative of any treatment-related health effect.

At necropsy, unilateral ovarian cysts were noted in 2/10 and 1/10 animals treated with SS0604.01 and 10000498, respectively. These findings are considered incidental and unrelated to treatment. No other macroscopic lesions were observed in any of the animals.

Under the conditions of this test, the acute oral LD50s of the test materials SS0592.01, SS0604.01, SS0605.01, SS0608.01, and 10000498 was estimated to be greater than 5 ml/kg in the female mouse.

IX. REFERENCES

1. Guide for the Care and Use of Laboratory Animals, DHHS Publication No. (NIH) 96-03, 1996.

_____ Date: _____

Elizabeth V. Weaver, B.A., DABT
Study Director
PGNCTL

PGNCTL Study No.:
B99-9010

Single Oral Dose Study
with SS0592.01, SS0604.01, SS0605.01, SS0608.01 and 10000498
in Mice with Limited Neurological Endpoints

TABLE 1
Mortality Summary

Test Material	Dose Level (ml/kg)	Mortality Result No. Died / No. Dosed
SS0592.01	5	0/10
SS0604.01	5	0/10
SS0605.01	5	0/10
SS0608.01	5	0/10
10000498	5	0/10

Single Oral Dose Study
with SS0592.01, SS0604.01, SS0605.01, SS0608.01 and 10000498
in Mice with Limited Neurological Endpoints

TABLE 2
Individual and Mean Body Weights and Body Weight Gains

Test Material	Animal Number	Day 1	Day 8		Day 15		Total
		Weight (g)	Weight (g)	Gain* (g)	Weight (g)	Gain (g)	Weight Gain[1] (g)
SS0592.01	251	23.7	24.5	0.8	24.7	0.2	1.0
	313	23.2	25.0	1.8	27.1	2.1	3.9
	316	24.6	25.4	0.8	27.8	2.4	3.2
	252	23.7	25.2	1.5	27.4	2.2	3.7
	280	22.7	24.8	2.1	25.9	1.1	3.2
	292	23.0	25.0	2.0	27.7	2.7	4.7
	264	23.7	26.7	3.0	27.5	0.8	3.8
	250	24.1	24.3	0.2	25.6	1.3	1.5
	308	23.3	24.6	1.3	25.3	0.7	2.0
	297	22.3	24.0	1.7	24.9	0.9	2.6
	Mean	23.4	25.0	1.5	26.4	1.4	3.0
	Std Dev	0.7	0.7	0.8	1.2	0.8	1.2
SS0604.01	267	24.5	25.4	0.9	26.1	0.7	1.6
	310	24.5	24.6	0.1	26.5	1.9	2.0
	275	24.2	27.1	2.9	30.1	3.0	5.9
	279	24.1	26.1	2.0	27.4	1.3	3.3
	274	23.9	25.0	1.1	26.4	1.4	2.5
	260	23.9	25.4	1.5	27.3	1.9	3.4
	273	23.7	26.2	2.5	27.7	1.5	4.0
	305	23.8	25.9	2.1	26.9	1.0	3.1
	285	23.8	26.7	2.9	27.2	0.5	3.4
	288	22.6	23.2	0.6	24.8	1.6	2.2
	Mean	23.9	25.6	1.7	27.0	1.5	3.1
	Std Dev	0.5	1.1	1.0	1.4	0.7	1.2
SS0605.01	293	25.4	26.5	1.1	29.0	2.5	3.6
	304	24.0	25.7	1.7	26.7	1.0	2.7
	281	23.7	25.1	1.4	26.1	1.0	2.4
	306	23.9	26.2	2.3	27.7	1.5	3.8
	289	24.2	25.7	1.5	25.3	-0.4	1.1
	303	24.1	26.1	2.0	27.1	1.0	3.0
	282	22.8	25.1	2.3	26.9	1.8	4.1
	311	23.2	24.1	0.9	24.0	-0.1	0.8
	307	22.8	23.8	1.0	25.0	1.2	2.2
	261	22.3	23.9	1.6	25.1	1.2	2.8
	Mean	23.6	25.2	1.6	26.3	1.1	2.7
	Std Dev	0.9	1.0	0.5	1.5	0.8	1.1

* Weight gain since previous weigh date

[1] Weight gain since study day 1

TABLE 2
Individual and Mean Body Weights and Body Weight Gains

Test Material	Animal Number	Day 1	Day 8		Day 15		Total
		Weight (g)	Weight (g)	Gain* (g)	Weight (g)	Gain (g)	Weight Gain[1] (g)
SS0608.01	262	24.2	25.9	1.7	28.4	2.5	4.2
	268	23.0	26.8	3.8	28.7	1.9	5.7
	266	24.1	27.5	3.4	30.0	2.5	5.9
	312	24.2	26.0	1.8	28.2	2.2	4.0
	295	23.3	24.8	1.5	26.2	1.4	2.9
	287	23.2	25.3	2.1	25.9	0.6	2.7
	300	22.9	25.2	2.3	26.9	1.7	4.0
	294	23.6	25.9	2.3	26.0	0.1	2.4
	314	22.8	25.3	2.5	25.4	0.1	2.6
	299	21.8	23.6	1.8	26.8	3.2	5.0
	Mean	23.3	25.6	2.3	27.3	1.6	3.9
	Std Dev	0.8	1.1	0.7	1.5	1.1	1.3
10000498	245	24.8	25.3	0.5	26.9	1.6	2.1
	278	24.9	25.5	0.6	27.8	2.3	2.9
	276	24.4	26.0	1.6	28.3	2.3	3.9
	315	23.2	25.2	2.0	27.0	1.8	3.8
	319	23.7	24.7	1.0	26.1	1.4	2.4
	259	23.2	26.0	2.8	27.8	1.8	4.6
	247	23.5	24.5	1.0	27.1	2.6	3.6
	270	23.1	24.3	1.2	25.7	1.4	2.6
	258	22.8	24.5	1.7	26.1	1.6	3.3
	249	22.4	24.3	1.9	26.5	2.2	4.1
	Mean	23.6	25.0	1.4	26.9	1.9	3.3
	Std Dev	0.8	0.7	0.7	0.8	0.4	0.8

* Weight gain since previous weigh date

[1] Weight gain since study day 1

Single Oral Dose Study
with SS0592.01, SS0604.01, SS0605.01, SS0608.01 and 10000498
in Mice with Limited Neurological Endpoints

TABLE 3
Individual Clinical Observations

Test Material	Animal Number	Clinical Observations	Presence of Observation										
			Day 1	Day 1 Interval (hrs.)							Day		
			Pre-Dose	0.0-2.0	2.5	3	3.5	4	6	8	2	3-6	7-15
SS0592.01	251	Normal	P	P	P	P	P	P	P	P	P	-	P
		Injured Left Hind Limb	-	-	-	-	-	-	-	-	-	P	-
	313	Normal	P	P	P	P	P	P	P	P	P	P	P
	316	Normal	P	P	P	P	P	P	P	P	P	P	P
	252	Normal	P	P	P	P	P	P	P	P	P	P	P
	280	Normal	P	-	P	P	P	P	P	P	P	P	P
		Locomotor Activity Increased	-	P	-	-	-	-	-	-	-	-	-
	292	Normal	P	P	P	P	P	P	P	P	P	P	P
	264	Normal	P	P	P	P	P	P	P	P	P	P	P
	250	Normal	P	P	P	P	P	P	P	P	P	P	P
	308	Normal	P	P	P	P	P	P	P	P	P	P	P
	297	Normal	P	P	P	P	P	P	P	P	P	P	P
SS0604.01	267	Normal	P	P	P	P	P	P	P	P	P	P	P
	310	Normal	P	-	P	P	P	P	P	P	P	P	P
		Ataxia	-	P -15/71[1]	-	-	-	-	-	-	-	-	-
		Loss of Righting Reaction	-	P-17/43	-	-	-	-	-	-	-	-	-
	275	Normal	P	-	P	P	P	P	P	P	P	P	P
		Ataxia	-	P-20/22	-	-	-	-	-	-	-	-	-
	279	Normal	P	P	P	P	P	P	P	P	P	P	P
	274	Normal	P	-	P	P	P	P	P	P	P	P	P
		Ataxia	-	P-20/20	-	-	-	-	-	-	-	-	-
	260	Normal	P	-	P	P	P	P	P	P	P	P	P
		Ataxia	-	P-21/16	-	-	-	-	-	-	-	-	-
	273	Normal	P	-	P	P	P	P	P	P	P	P	P
		Ataxia	-	P-15/33	-	-	-	-	-	-	-	-	-
	305	Normal	P	-	P	P	P	P	P	P	P	P	P
		Ataxia	-	P-16/29	-	-	-	-	-	-	-	-	-
	285	Normal	P	-	P	P	P	P	P	P	P	P	P
		Ataxia	-	P-13/47	-	-	-	-	-	-	-	-	-
		Loss of Righting Reaction	-	P-21/03	-	-	-	-	-	-	-	-	-
	288	Normal	P	P	P	P	P	P	P	P	P	P	P

P = Observation Present
- = Observation Not Present

[1] For clinical signs of ataxia and loss of righting reflex, numbers occurring after the P indicate Time of Onset (min. post-dose)/Duration (min.)

PGNCTL Study No.:
B99-9010

Single Oral Dose Study
with SS0592.01, SS0604.01, SS0605.01, SS0608.01 and 10000498
in Mice with Limited Neurological Endpoints

TABLE 3
Individual Clinical Observations

Test Material	Animal Number	Clinical Observations	Presence of Observation										
			Day 1	Day 1 Interval (hrs.)							Day		
			Pre-Dose	0.0-2.0	2.5	3	3.5	4	6	8	2	3-6	7-15
SS0605.01	293	Normal	P	P	P	P	P	P	P	P	P	P	P
	304	Normal	P	P	P	P	P	P	P	P	P	P	P
	281	Normal	P	P	P	P	P	P	P	P	P	P	P
	306	Normal	P	P	P	P	P	P	P	P	P	P	P
	289	Normal	P	-	P	P	P	P	P	P	P	P	P
		Feces Soft	-	P	-	-	-	-	-	-	-	-	-
	303	Normal	P	P	P	P	P	P	P	P	P	P	P
	282	Normal	P	P	P	P	P	P	P	P	P	P	P
	311	Normal	P	P	P	P	P	P	P	P	P	P	P
	307	Normal	P	P	P	P	P	P	P	P	P	P	P
	261	Normal	P	P	P	P	P	P	P	P	P	P	P
SS0608.01	262	Normal	P	P	P	P	P	P	P	P	P	P	P
	268	Normal	P	P	P	P	P	P	P	P	P	P	P
	266	Normal	P	P	P	P	P	P	P	P	P	P	P
	312	Normal	P	P	P	P	P	P	P	P	P	P	P
	295	Normal	P	P	P	P	P	P	P	P	P	P	P
	287	Normal	P	P	P	P	P	P	P	P	P	P	P
	300	Normal	P	P	P	P	P	P	P	P	P	P	P
	294	Normal	P	P	P	P	P	P	P	P	P	P	P
	314	Normal	P	P	P	P	P	P	P	P	P	P	P
	299	Normal	P	P	P	P	P	P	P	P	P	P	P
10000498	245	Normal	P	P	P	P	P	P	P	P	P	P	P
	278	Normal	P	P	P	P	P	P	P	P	P	P	P
	276	Normal	P	P	P	P	P	P	P	P	P	P	P
	315	Normal	P	P	P	P	P	P	P	P	P	P	P
	319	Normal	P	P	P	P	P	P	P	P	P	P	P
	259	Normal	P	P	P	P	P	P	P	P	P	P	P
	247	Normal	P	P	P	P	P	P	P	P	P	P	P
	270	Normal	P	P	P	P	P	P	P	P	P	P	P
	258	Normal	P	P	P	P	P	P	P	P	P	P	P
	249	Normal	P	P	P	P	P	P	P	P	P	P	P

P = Observation Present
- = Observation Not Present

[1] For clinical signs of ataxia and loss of righting reflex, numbers occurring after the P indicate Time of Onset (min. post-dose)/Duration (min.)

APPENDIX A

SINGLE ORAL DOSE STUDY WITH SS0592.01, SS0604.01, SS0605.01, SS0608.01 AND 10000498 IN MICE WITH LIMITED NEUROLOGICAL ENDPOINTS

FINAL PROTOCOL

PGNCTL Study No. B99-9010
P&G DRD No. SSBTS98.020-50419

Procter & Gamble Non Clinical Testing Laboratory (PGNCTL)
Miami Valley Laboratories
11810 E. Miami River Road
Ross, Ohio 45061

Elizabeth V. Weaver, B.A., DABT
Study Director

Conducted for

Nancy Gorelick, Ph.D.
Sponsor Representative
Fabric and Home Care
Ivorydale Technical Center
5299 Spring Grove Ave.
Cincinnati, OH 45217
Phone: (513) 627-6520
FAX: (513) 627-5182

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STUDY IDENTIFICATION

Single Oral Dose Study
with SS0592.01, SS0604.01, SS0605.01, SS0608.01
and 10000498 in Mice
with Limited Neurological Endpoints

Test Substance Identification Number(s) (TSIN)	SS0592.01 SS0604.01 SS0605.01 SS0608.01 10000498

I. RESPONSIBILITIES

A.	Sponsor	The Procter & Gamble Company Cincinnati, OH 45217
B.	Sponsor Representative	Nancy Gorelick, Ph.D. Ivorydale Technical Center 5299 Spring Grove Ave. Cincinnati, OH 45217 Phone: (513) 627-6520 FAX: (513) 627-5182
C.	Alternative Sponsor Contact	Mark Lafranconi, Ph.D. Ivorydale Technical Center 5299 Spring Grove Ave. Cincinnati, OH 45217 Phone: (513) 627-4435 FAX: (513) 627-5182
D.	Testing Location	PGNCTL The Procter & Gamble Company Miami Valley Laboratories 11810 E. Miami River Road Ross, OH 45061 Phone: (513) 627-1107 FAX: (513) 627-0958
E.	PGNCTL Study Director	Elizabeth V. Weaver, B.A., DABT The Procter & Gamble Company Miami Valley Laboratories 11810 E. Miami River Road Ross, OH 45061 Phone: (513) 627-2980 FAX: (513) 627-0958

II. PROPOSED STUDY SCHEDULE

A. Initiation of In-Life Phase (Day 1 - First day of dosing): October 29, 1998

B. Estimated Completion of In-Life Phase (Day of last euthanasia): November 13, 1998

C. Estimated Draft Report Date (3 weeks from In-Life Completion): December 4, 1998

III. PURPOSE AND REGULATORY STATUS

A. Study

Acute Oral Toxicity Study with SS0592.01, SS0604.01, SS0605.01, SS0608.01 and 10000498 in Mice with Additional Neurological Examinations.

B. Purpose

The objective of the study is to assess the short-term toxicity, specifically neurotoxicity as determined by examination of the endpoints of ataxia and loss of righting reaction, of a test article in mice when administered by gavage as a single oral dose. This study is intended to provide information on the potential hazards of the test article with respect to oral exposure. Data from this study may serve as a basis for classification and/or labeling of the test article.

IV. TEST ARTICLE IDENTIFICATION

A. Test Article

1. Test Substance Identification Number(s) (TSIN) and physical characteristics.

TSIN	Color	Physical Form	Expiration Date
SS0592.01	slightly yellow	liquid	10/13/99
SS0604.01	opaque	liquid	9/99
SS0605.01	opaque	liquid	9/99
SS0608.01	slightly yellow	liquid	10/99
10000498	colorless	liquid	7/14/99

2. Purity

Purity Information (including under test conditions) is the responsibility of the Sponsor Representative.

3. Stability

Stability information (including under test conditions) is the responsibility of the Sponsor Representative.

4. Storage Conditions

All test articles listed above will be stored at room temperature based on the Sponsor Representative's instructions.

5. Characteristics

Information on synthesis methods, composition, or other characteristics that define the test article is the responsibility of the Sponsor Representative.

B. Retention Samples

A retention sample (approximately 2 mL or 2 g) of each test article will be taken on the day of treatment and stored at room temperature. These samples will be transferred to the Sponsor Representative after completion of the in-life phase and retention is the responsibility of the Sponsor Representative.

C. Disposition of Test Articles

Any remaining test articles will be returned after authorization from the Sponsor Representative. Test articles will be returned to:

Mary Marrero
F&HC PSR&AS C1N39E
Sharon Woods Technical Center
11510 Reed Hartman Highway
Cincinnati, OH 45241

D. Handling Precautions

Safety data regarding the test articles should be provided by the Sponsor Representative [Material Safety Data Sheet (MSDS) or equivalent, if available]. The Study Director will review the test article safety data with study personnel. Any question concerning this information should be referred to the Study Director. Additional safety and handling information may be provided by the Study Director and/or Sponsor Representative. Minimum safety requirements include the use of safety glasses, impervious gloves, and laboratory wear.

E. Method of Test Article Preparation

The test articles are liquids and will be administered as received according to the Sponsor Representative's instructions. Selected dosages will be achieved by varying the dosage volume. The dose volume will be 5 ml/kg body weight. The test article will be prepared and/or dispensed fresh on the day of dosing. The method of preparation will be documented in the raw data and presented in the final report.

V. TEST SYSTEM

A. Justification of the Test System

1. The mouse is a preferred species for acute oral toxicity testing by various U.S. and international regulatory agencies.

2. The ICR:CD-1® mouse has been shown to be sensitive to the toxic effects of a variety of drugs and chemicals. Therefore, this species and strain is a reasonable alternative to larger mammals for acute toxicity testing of drugs and chemicals for human safety assessment.

3. The ICR:CD-1® mouse has been used extensively for toxicological testing. Thus, data from this study may be compared and contrasted to other studies performed in ICR:CD-1® mice.

4. Historical information concerning ICR:CD-1®mice is available in the published literature.

5. Healthy, outbred ICR:CD-1® mice may be obtained from reliable, USDA approved and regulated suppliers.

6. The laboratory mouse may be safely handled and manipulated by trained technical personnel.

PGNCTL has conducted literature searches through Medline, Toxline and Biological Abstracts and there are no generally accepted validated alternatives to this test.

B. Justification of the Route of Exposure and Number of Animals

1. Oral administration of the test article was selected since this is a potential route of human exposure.

2. Since mice are not able to regurgitate, orally administered substances may be accurately delivered without the possible confounding factor of loss of material in vomitus.

3. This test is a modification of the Limit test. Five animals/sex are normally used, however, this test will utilize 10 female mice per test article.

C. Description

1. Species

Mouse

2. Strain

ICR:CD-1®

3. Source

Harlan Sprague Dawley, Inc.
Indianapolis, IN

Another USDA approved supplier may be substituted, and the supplier used will be documented in study records.

4. Age and Body Weight Range

Animals will be ordered to arrive at approximately 6 weeks of age. Young adult female mice, approximately 20 to 35 g (weight prior to fasting), will be used. Body weights will be documented in study records. The range of body weights in the study will be within ± 20% of the mean weight.

5. Number of Animals/Sex on Study

10 females for each test article.

D. Method of Identification

Metal ear tags displaying unique identification numbers will be used to individually identify the animals. Cage cards displaying at least the study number, ear tag number, and sex will be affixed to each cage.

E. Animal Husbandry

1. Housing

The animals will be housed individually in clear plastic shoebox cages with hardwood bedding at receipt and throughout the study with one exception. Immediately after dosing, animals will be housed in clear plastic shoebox cages without bedding for the first two hours post-dose so that observations for ataxia will be readily observable. Hardwood bedding will be replaced at the end of this initial two hour observation period. All housing and care will be based on the standards recommended by the current Guide for the Care and Use of Laboratory Animals [1].

2. Environment

Animal rooms will be maintained at room temperature and relative humidity ranges of 72 ± 5°F and 50 ± 20%, respectively. Environmental control equipment will be monitored and adjusted as necessary to minimize fluctuations in the animal room environment. A 12-hour light/12-hour dark cycle will be maintained in the animal room environment, and the room ventilation will be set to produce approximately 10 air changes/hour. Room temperature and humidity will be recorded a minimum of once daily. Pre-fasted body weights and food removal may be done during the 12-hour dark cycle. If this occurs, the lights will be turned on in the animal room for a limited period of time (approximately one hour) to permit these procedures to be performed safely.

3. Food

PMI Certified Rodent Chow #5002 (Purina Mills, Inc.) will be provided ad libitum to the animals throughout the study except for an overnight period prior to test article administration and for approximately two hours post-dose (approximately 8-12 hours total). The lot number of each batch of diet used during the study will

be recorded. The feed is analyzed by the supplier for nutritional components and environmental contaminants. Dietary limitations for various environmental contaminants, including heavy metals, pesticides, polychlorinated biphenyls and total aflatoxin are set by the manufacturer. Within these limits, there are no environmental contaminants reasonably expected in the diet which would interfere with the conduct of the study. Results of dietary analyses (Certificates of Analysis) are provided by the manufacturer for each lot of diet. These will be maintained by the PGNCTL.

4. Water

Municipal tap water following treatment by reverse osmosis will be available ad libitum throughout the study, with the exception of approximately the first two hours post-dose, and will be supplied either by bottle or by an automatic watering system. Monitoring of the drinking water for contaminants will be conducted periodically and the records will be maintained by the testing facility. Levels of contaminants which may be present are not expected to compromise the purpose of the study. The water meets the standards specified under the EPA National Drinking Water Regulations (40 CFR, Part 141).

5. Acclimation

Upon receipt, the animals will be removed from the shipping cartons, weighed and individually housed in shoebox cages (one animal/cage). The animals will be examined by qualified personnel, identified by metal ear tags, and ear tag numbers recorded. Animals will be acclimated to the laboratory conditions for a minimum of 72 hours. The animals will be observed daily for overt physical or behavioral abnormalities, moribundity, and mortality.

6. Animal Selection

Only animals meeting health and body weight requirements, and exhibiting normal behavior, will be chosen for study use. The animals chosen for study use will be arbitrarily selected from healthy stock animals to avoid potential bias. All animals will receive a detailed pretest observation period prior to dosing. Females will be nulliparous and nonpregnant.

VI. EXPERIMENTAL DESIGN AND PROCEDURES

A. Study Group Design

The animals will be assigned to groups as follows:

Group	Test Article	Dose Level (ml/kg)[a]	Number of Animals
1	SS0592.01	5 mL/kg	10
2	SS0604.01	5 mL/kg	10
3	SS0605.01	5 mL/kg	10
4	SS0608.01	5 mL/kg	10
5	10000498	5 mL/kg	10

• Additional dose levels consisting of 10 females may be added based on the results of the initial dose level. These dose levels may be varied using a multiplier of 1.3 following an "up/down" study procedure. Justification for the additional dose levels will be provided by protocol amendment.

B. Rationale for Dosage Level Selection

The dose level(s) utilized will be documented in the raw data and presented in the final report. The initial dose level(s) will be chosen by the Sponsor Representative and Study Director.

1. Limit Test

A Limit Test will be conducted using ten females/test article at a single high dose level (e.g., 5 ml/kg). Additionally, this test will evaluate endpoints of neurotoxicity, specifically ataxia and righting reaction. In event of significant mortality, additional dose levels may be conducted and will be documented as an amendment to the protocol.

C. Dosing Duration

The animals chosen for use on study will be weighed prior to randomization and fasted approximately 8 to 10 hours prior to dosing. At the end of this fasting period, the animals will be weighed and the appropriate individual doses will be calculated based on this fasted body weight. The dose preparation will be administered in a single oral dose at a volume of 5 ml/kg. The dose preparation will be administered using a ball tipped stainless steel gavage needle attached to an appropriately sized syringe. Animals will be returned to ad libitum feeding approximately 2 hours after dosing. Dosing will be staggered over a two day period. Groups will be dosed in order, five female mice per test article per day. The first five animals assigned to each test article group will be dosed and observed on October 29, 1998. The remaining five animals in each test article group will be dosed and observed on October 30, 1998.

D. Randomization

Animals showing no clinical signs of ill health will be weighed prior to fasting in the order of cage position in the room and randomized approximately 12 to 24 hours prior to dosing. After weighing, animals with acceptable body weights will be ordered by weight in descending order.

If there are more acceptable animals than are needed to fill the study groups, the extra animals with the largest and/or smallest body weights will be eliminated as deemed appropriate and documented. The remaining 50 animals will be distributed into 5 groups of 10 female animals each using a stratified randomization procedure based on body weight as described below. Starting with the heaviest 5 animals and taking each block of 5 animals arranged by weight, the animals will be randomized into groups using a random number table. Each block of 5 animals will be assigned consecutive numbers for randomization purposes. These block number assignments will be used to compare to the random number table [2] to determine the random assignment of animals within each block to the dose groups.

E. Body Weights

Body weights will be obtained at receipt and prior to randomization. Individual body weights will be obtained for each animal, and the weight variation of the animals within the

study should not exceed ± 20% of the mean weight prior to randomization. Body weights will be obtained for all surviving animals 7 and 14 days post-dose, and for animals found dead or euthanized for humane purposes after Study Day 1.

F. Clinical Observations

Animals will be observed pre-dose (1-15 minutes prior to dosing), continuously for 2 hours post-dose, approximately 2.5, 3.0, 3.5, 4.0, 6.0, and 8.0 hours post-dose, and daily thereafter through fourteen days post-dose (approximately the same time each day). Each observation interval will include specific evaluations for ataxia and righting reaction endpoints. The procedures for these neurological assessments are described in Appendix 1. Routine examinations for clinical observations will be done concurrently with weekly body weights. Other clinical observations will be recorded if observed through fourteen days post-dose.

A general health/mortality check will be performed twice daily (in the morning and in the afternoon) for all animals on study.

G. Unscheduled Deaths and Euthanasia

Animals dying or euthanized in a moribund condition during the study period will be necropsied. For animals found dead, the date of death will be considered to be the date they are found. Animals will be necropsied according to the procedure described below under Anatomic Pathology.

H. Scheduled Euthanasia

All animals surviving to the end of the study will be necropsied according to the procedure described below under Anatomic Pathology. Prior to necropsy, animals will be euthanized by carbon dioxide inhalation. The date of death will be recorded.

I. Anatomic Pathology

All animals submitted for necropsy will receive a macroscopic evaluation made under the supervision of a veterinary pathologist. The evaluation will be limited to orifices, external surfaces of the body, and the cranial, thoracic, abdominal, and pelvic cavities and their contents. The order of necropsy for animals surviving through fourteen days post-dose will be alternated by group, starting with group one through group five, consecutively, and then repeating until all animals scheduled for that day have been completed. Tissues will not be collected and microscopic evaluation will not be performed unless considered necessary by the supervising pathologist.

VII. PROTOCOL AMENDMENT

Alterations to this protocol may be made as the study progresses. If changes in the protocol are made, a protocol amendment will be prepared by the Study Director and signed by the Study Director and Sponsor Representative.

VIII. DATA REPORTING

Copies of the draft study report will be reviewed by the Study Director, the Quality Assurance Unit, and others as requested. The final study report will be signed by the Study Director and copies submitted to the Sponsor Representative and others as requested. The final study report will include all information necessary to provide a complete and accurate description and evaluation of the experimental procedures and results.

The report will include at least the following information and data:

- Table of Contents
- Regulatory Compliance
- Summary
- Introduction
- Experimental Design and Test Procedures
- Presentation and Discussion of Results
- Conclusion
- References
- Data Tables
- Protocol and Amendments
- PGNCTL Personnel Responsibilities

In addition to the above data, the following specifications will be incorporated into the report:

- Number of animals including body weight at start of study
- Date of death of individual animals
- Number of animals displaying signs of toxicity
- Description of toxic effects
- Time of onset and duration of any neurotoxicity observations (ataxia and loss of righting reaction).
- Necropsy findings
- Relationships, if any, between dose and incidence/severity/reversibility of clinical observations

IX. ANALYSIS OF DATA

No statistical analysis of the data will be required. Body weight means and standard deviations will be calculated.

X. MAINTENANCE OF RAW DATA, RECORDS AND SPECIMENS

All original data, magnetically encoded records, specimens and reports from this study are the property of the Sponsor. These materials will be available at PGNCTL to facilitate auditing of the study during its progress and prior to acceptance of the final report. All original paper data and the final report will be archived in the PGNCTL archives (Central Records-MVL) for a period of 20 years. The Sponsor will be contacted prior to the final disposition of these items. Any histology specimens obtained during this study will be forwarded to Pathology Associates, Inc., Cincinnati, Ohio.

XI. REGULATORY COMPLIANCE

This study will be conducted in accordance with the United States Environmental Protection Agency's Good Laboratory Practice Standards, 40 CFR 792 with the exception that analysis of the prepared test article mixtures (if applicable) for concentration, homogeneity/solubility, and stability will not be conducted.

XII. QUALITY ASSURANCE

The study will be inspected at least once during the in-life phase by the PGNCTL Quality Assurance Unit to assure compliance with Good Laboratory Practice regulations, PGNCTL's Standard Operating Procedures and for conformance with the protocol and protocol amendments. The draft report will be audited, to ensure that it completely and accurately describes the test procedures and results of the study, prior to the Study Director signing the report and subsequent submission to the Sponsor Representative.

XIII. USDA ANIMAL WELFARE COMPLIANCE STATEMENT

This study will comply with all applicable sections of the Final Rules of the Animal Welfare Act regulations (9 CFR) and the Public Health Service Policy on Humane Care and Use of Laboratory Animals (OPRR, NIH, 1986). Wherever possible, procedures used in this study have been designed to avoid or minimize discomfort, distress and pain to animals. All methods are described in this study protocol or in written laboratory standard operating procedures. These procedures are based on the most currently available technologies concerning proper laboratory animal use and management. Methods of euthanasia used during this study are in conformance with the above referenced regulations and the American Veterinary Medical Association Panel on Euthanasia [3]. This protocol has been reviewed and approved by The Procter & Gamble Company's Institutional Animal Care and Use Committee (IACUC) for a maximum of 60 animals.

This study is being conducted to monitor several endpoints including clinical effects, body weight effects, lethality, neurotoxicity and reversible toxicity. Since lethality and reversible toxicity are specific endpoints in this evaluation, administration of sedatives, tranquilizers and/or analgesics will not be routinely undertaken due to their possible interference on evaluation of these endpoints. However, if the animals progress to a moribund condition, the Study Director will contact the Facility Veterinarian to help appraise the condition of the animals and assess whether recovery is unlikely and that no relevant scientific data would be gained by maintaining the animals on study, then the Sponsor Representative will be contacted and informed that euthanasia of the moribund animals is recommended for humane reasons. In the event that the Sponsor Representative cannot be contacted, the Study Director and/or Facility Veterinarian may authorize euthanasia of the moribund animals.

XIV. DECLARATION OF INTENT

This study will be listed on the PGNCTL Quality Assurance Master Schedule as a nonregulated study.

XV. PROTOCOL APPROVAL

The Sponsor Representative's signature constitutes authorization to conduct the study and documents for the Study Director that there are no acceptable non-animal alternatives for this study, that this study does not unnecessarily duplicate previous studies, and that this study is required for regulatory purposes and/or human safety assessment.

Nancy Gorelick, Ph.D.
Study Representative

Date: 10/28/98

Elizabeth V. Weaver, B.A., DABT
Study Director

Date: 10/28/98

XIV. REFERENCES

1. Guide for the Care and Use of Laboratory Animals, DHHS Publication No. (NIH) 96-03, 1996.
2. F. James Rohlf and Robert R. Sokal. 1981 2nd Edition. *Statistical Tables.*W. H. Freeman and Company.pp71-75.
3. Report of the American Veterinary Medical Assoc. Panel on Euthanasia, JAVMA, Vol. 202, No. 2, pp. 229-249, January 15, 1993.

Protocol Appendix A
Neurological Assessment

The following neurological assessments will be made prior to dosing (approximately 1-15 minutes prior to dosing), continuously for 2 hours, approximately 2 ½, 3, 3 ½, 4, 6, and 8 hours post-dose. These neurological assessments will also be made daily thereafter through fourteen days post-dose. Daily observations will be conducted at the approximate same time each day.

All neurological observations will be conducted while the animals are in their individual plastic shoebox cages.

Ataxia: Ataxia is defined by reeling, lurching, or staggering gait. The term ataxia should not be used as a "catch all" term to describe impaired movement or weakness.

> Ataxia will be evaluated by observing spontaneous locomotor activity. Each animal will be prompted to walk, if necessary.

Righting Reaction: Animals exhibiting abnormal behavior will be tested for the righting reaction. Righting reaction will be assessed by placing the animal on its back and observing the return to a normal weight-bearing posture.

Protocol Amendment Number 1

Study Title: Single Oral Dose Study with SS0592.01, SS0604.01, SS0605.01, SS0608.01, and 10000498 in Mice with Limited Neurological Endpoints

Study Number: B99-9010

Date: November 19, 1998

Protocol Change: See protocol, page 4 under Section IV. Test Article Identification, TSIN, SS0592.01, SS0604.01 and SS0605.01, and corresponding expiration dates.

Expiration dates for 3 of 5 test articles were incorrectly reported as follows:

TSIN	Expiration Date
SS0592.01	10/13/99
SS0604.01	9/99
SS0605.01	9/99

Corrected information is:

TSIN	Expiration Date
SS0592.01	9/99
SS0604.01	10/13/99
SS0605.01	10/13/99

Reason for change: The expiration dates for these test articles as reported in the original protocol were incorrect. The correct information is being added by this protocol amendment.

Nancy Gorelick, Ph.D.
Study Representative

Date: 12-8-98

Elizabeth V. Weaver, B.A., DABT
Study Director

Date: 11-19-98

Protocol Amendment Number 2

Study Title: Single Oral Dose Study with SS0592.01, SS0604.01, SS0605.01, SS0608.01, and 10000498 in Mice with Limited Neurological Endpoints

Study Number: B99-9010

Date: December 21, 1998

Protocol Change: See protocol, cover page under P&G DRD Number.

P&G DRD No. SSBTS98.020-50419

Corrected information is:

P&G DRD No. SSBTS98.020
SAF 265-50419

Reason for change: The DRD number was not listed correctly in the original protocol. An additional category entitled "SAF" should have been included, with the reference "265-50419". The correct information is being added by this protocol amendment and will be reflected in the final report.

Nancy Goreick, Ph.D.
Study Representative

Date: 1/4/99

Elizabeth V. Weaver, B.A., DABT
Study Director

Date: 12/21/98

APPENDIX B

PATHOLOGY REPORT

There were 10 female mice each in five treatment groups euthanized and necropsied at the termination of the study (14 days post-dose). The necropsy evaluation was limited to orifices, external surfaces of the body, and the cranial, thoracic, abdominal, and pelvic body cavities and their contents. In treatment groups SS0604.01 and 10000498, 2/10 and 1/10 animals, respectively, exhibited unilateral ovarian cysts. These findings were considered incidental and unrelated to treatment. No other macroscopic lesions were observed in any of the animals. Individual macroscopic necropsy observations are presented in the attached Table 1. Pathology data is archived with study records.

_____ Date_____

Andrew S. Fix, Ph.D., D.V.M., DACVP
Study Pathologist

PGNCTL Study No.:
B99-9010

Single Oral Dose Study
with SS0592.01, SS0604.01, SS0605.01, SS0608.01 and 10000498
in Mice with Limited Neurological Endpoints

Table 1
Individual Gross Necropsy Observations

Test Material	Animal Number	Necropsy Observations
SS0592.01	251	No abnormalities detected
	313	No abnormalities detected
	316	No abnormalities detected
	252	No abnormalities detected
	280	No abnormalities detected
	292	No abnormalities detected
	264	No abnormalities detected
	250	No abnormalities detected
	308	No abnormalities detected
	297	No abnormalities detected
SS0604.01	267	No abnormalities detected
	310	No abnormalities detected
	275	No abnormalities detected
	279	No abnormalities detected
	274	No abnormalities detected
	260	No abnormalities detected
	273	No abnormalities detected
	305	Cyst left ovary, No other abnormalities detected
	285	No abnormalities detected
	288	Cyst left ovary, No other abnormalities detected
SS0605.01	293	No abnormalities detected
	304	No abnormalities detected
	281	No abnormalities detected
	306	No abnormalities detected
	289	No abnormalities detected
	303	No abnormalities detected
	282	No abnormalities detected
	311	No abnormalities detected
	307	No abnormalities detected
	261	No abnormalities detected
SS0608.01	262	No abnormalities detected
	268	No abnormalities detected
	266	No abnormalities detected
	312	No abnormalities detected
	295	No abnormalities detected
	287	No abnormalities detected
	300	No abnormalities detected
	294	No abnormalities detected
	314	No abnormalities detected
	299	No abnormalities detected

PGNCTL Study No.:
B99-9010

Single Oral Dose Study
with SS0592.01, SS0604.01, SS0605.01, SS0608.01 and 10000498
in Mice with Limited Neurological Endpoints

Table 1
Individual Gross Necropsy Observations

Test Material	Animal Number	Necropsy Observations
10000498	245	No abnormalities detected
	278	No abnormalities detected
	276	No abnormalities detected
	315	No abnormalities detected
	319	No abnormalities detected
	259	No abnormalities detected
	247	No abnormalities detected
	270	No abnormalities detected
	258	No abnormalities detected
	249	Cyst right ovary - fluid red, No other abnormalities detected

APPENDIX C

PGNCTL PERSONNEL RESPONSIBILITIES

John A. Wisler, Ph.D., DABT	Senior Scientist
Elizabeth V. Weaver, B.A., DABT	Study Director, Associate Scientist
Sharon B. Stuard, M.S.	Associate Scientist
Cindy A. Blanton, B.S.	Senior Research Associate
Frank R. Lefever, A.S.	Senior Research Associate
Kara E. Woeller, B.S.	Research Associate
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